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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/293,670	04/16/1999	JOSEPH FISHER	RIGL-036CIP	5176

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EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 10/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/293,670	FISHER ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-36* is/are pending in the application.

4a) Of the above claim(s) *27-29, 31 and 33-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-26, 30 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/24/2006 has been entered.

Status of Claims

Claims 17-36 are under examination.

Claims 26 (in part), 27-29. 31, 32 (in part) and claims 33-36 are withdrawn from consideration as being directed to non-elected inventions and species.

Claims 17-26, 30 and 32 (with respect to the elected species) are under examination.

Withdrawn Rejection

In view of applicants' telephonic conversation on July 19, 2006 with the examiner's supervisor, Peter Paras, the rejection under 35 USC 112, first paragraph is withdrawn.

Also, in view of the amendment to claim 32, the new matter rejection under 35 USC 112, first paragraph is withdrawn.

Likewise, the rejection under 35 USC second paragraph under paragraphs A-D is withdrawn.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17-26, 30 and 32, as amended, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claim 17 is unclear as to whether the population of cells contain each a library of vectors expressing each a different bioactive agents. It is further indefinite whether each of the population of cells are of the same or different type of cells such as sorting based on the at least five parameters is achieved. It is ambiguous as to whether the step of sorting the population of cells is based on the same at least five parameters or different five parameters. If different, the differentiating characteristic(s) of each of the at least 5 parameters in each cell to enable sorting by FACS. It is indefinite and confusing as to the kind or terms of the different phenotypic alterations made by each of the different

library of vectors, especially when each cell is different. It is unclear as to the difference between "expression of a cell surface receptor" from "expression of a receptor ***gent.*** Receptor ***gent*** is misspelled.

2. Claim 32 is unclear as to how it further limits the base claim method. The base claim method does not recite for a comparison with a positive control or that the agent is p21 such that a comparison can be made. It is unclear from the method steps of the base claim how the p21 is used as a positive control. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Double Patenting

Claims 17-26, 30 and 32, as amended, are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 and 5 of Application No. 09/157,748 (now U.S. Patent No. 6,461,813) or over application S.N. 09/062,330 (now US Patent No. 6,897,031) for reasons of record.

Response to Arguments

Applicants requested that this rejection be held in abeyance until allowable subject matter is identified in this application.

In reply, in the absence of a terminal disclaimer, the rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 17-24, 30 and 32, as amended, are rejected under 35 U.S.C. 102(e) as being anticipated by Nolan et al (USP 6455247). (Note that at the time of filing of the earliest filed application S.N. 4/17/1998 to which applicants are claiming priority, the Nolan reference is assigned to a different assignee i.e., The Board of Trustees of the Leland Stanford Junior

University. Assignment to Rigel is made after the invention was made i.e., 2001.)

Nolan et al discloses at col. 21, line 30 up to col. 22, line 18:

> The methods of the present invention comprise introducing a molecular library of randomized candidate nucleic acids into a plurality of cells, a cellular library. Each of the nucleic acids comprises a different, generally randomized, nucleotide sequence. The plurality of cells is then screened, as is more fully outlined below, for a cell exhibiting an altered phenotype. The altered phenotype is due to the presence of a transdominant bioactive agent.
>
> By "altered phenotype" or "changed physiology" or other grammatical equivalents herein is meant that the phenotype of the cell is altered in some way, preferably in some detectable and/or measurable way. As will be appreciated in the art, a strength of the present invention is the wide variety of cell types and potential phenotypic changes which may be tested using the present methods. Accordingly, any phenotypic change which may be observed, detected, or measured may be the basis of the screening methods herein. Suitable phenotypic changes include, but are not limited to: gross physical changes such as changes in cell morphology, cell growth, cell viability, adhesion to substrates or other cells, and cellular density; changes in the expression of one or more RNAs, proteins, lipids, hormones, cytokines, or other molecules; changes in the equilibrium state (i.e. half-life) or one or more RNAs, proteins, lipids, hormones, cytokines, or other molecules; changes in the localization of one or more RNAs, proteins, lipids, hormones, cytokines, or other molecules; changes in the bioactivity or specific activity of one or more RNAs, proteins, lipids, hormones, cytokines, receptors, or other molecules; changes in the secretion of ions, cytokines, hormones, growth factors, or other molecules; alterations in cellular membrane potentials, polarization, integrity or transport; changes in infectivity, susceptability, latency, adhesion, and uptake of viruses and bacterial pathogens;

etc. By "capable of altering the phenotype" herein is meant that the bioactive agent can change the phenotype of the cell in some detectable and/or measurable way.

The altered phenotype may be detected in a wide variety of ways, as is described more fully below, and will generally depend and correspond to the phenotype that is being changed. Generally, the changed phenotype is detected using, for example: microscopic analysis of cell morphology; standard cell viability assays, including both increased cell death and increased cell viability, for example, cells that are now resistant to cell death via virus, bacteria, or bacterial or synthetic toxins; standard labeling assays such as fluorometric indicator assays for the presence or level of a particular cell or molecule, including FACS or other dye staining techniques; biochemical detection of the expression of target compounds after killing the cells; etc. In some cases, as is more fully described herein, the altered phenotype is detected in the cell in which the randomized nucleic acid was introduced; in other embodiments, the altered phenotype is detected in a second cell which is responding to some molecular signal from the first cell.

Nolan discloses at col. 23, line 18 to line 33:

In a preferred embodiment, once a cell with an altered phenotype is detected, the cell is isolated from the plurality which do not have altered phenotypes. This may be done in any number of ways, as is known in the art, and will in some instances depend on the assay or screen. Suitable isolation techniques include, but are not limited to, FACS, lysis selection using complement, cell cloning, scanning by Fluorimager, expression of a "survival" protein, induced expression of a cell surface protein or other molecule that can be rendered fluorescent or taggable for physical isolation; expression of an enzyme that changes a non-fluorescent molecule to a fluorescent one; overgrowth against a background of no or slow growth; death of cells and isolation of DNA or other cell vitality indicator dyes, etc.

See further the Examples which describes the method in detail.

Claim Rejections - 35 USC § 103

Claims 17-25, 30 and 32, as amended, are rejected under under 35 U.S.C. 103(a) as being obvious over Nolan in view of Jia-ping (Chinese Journal of Physical Medicine) or Ryan et al (Jrnl. of Immunological Methods).

Nolan is discussed above. Nolan does not disclose a method in which the cellular phenotype is exocytosis. However, Jia-ping discloses a method of sorting cells by multi-parameter sorting technique using flow cytometer including exocytosis. The method provides for an increased of purity of the divided cell and further information of the different cell subpopulations that can be obtained (page I). Ryan discloses that gating on log 90 degree light scatter (i.e., exocytosis) and log red fluorescence reduced the incidence of nonspecific binding using multiple flow cytometric parameters, page 115 and pages 120, Table 1 up to page 127. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to determine the exocytosis phenotype change in the method of Nolan in the manner as taught by either Jia-ping or Ryan. One having ordinary skill in the art would have been motivated to measure exocytosis for the advantages taught by Ryan or Jia-ping, above. Furthermore, while Nolan does not positively recite said exocytosis as the cellular phenotype however, it is considered

that the process of Nolan is obviously an exocytosis since cellular excretion or discharge of a substance from the cell, occurs as a result of fusion of membranes.

[Note that applicants' arguments are moot in view of the new ground of rejection, above. However, the declaration of Dr. Fisher under 35 U.S.C. § 1.131, as applied to the above Nolan reference has been considered. Exhibits A-C submitted in the declaration by Dr. Fisher describes method directed only to exocytosis phenotype alterations and measurement of the five parameters as it relates to exocytosis. The claims are not restricted to said exocytosis phenotype rather to the other broad phenotypes changes such as cell cycle, apoptosis, expression of a cell surface receptor and expression of a receptor agent. Declarant's work on the single phenotypic alteration by exocytosis is not sufficient as evidence that applicants are in possession of the broad claimed phenotypic changes prior to the priority date of 4/17/98.]

Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nolan in view of Jia-ping (Chinese Journal of Physical Medicine) or Ryan et al (Jrnl. of Immunological Methods as applied to claims 17-25, 30 and 32 above, and further in view

of Hide et al(Jrnl. of Cell Biology) and applicants' disclosure of admitted art.

Nolan is discussed, above. Nolan discloses FACS means of measuring the altered cellular phenotype except the claimed recitation that the exocytosis is measured by annexin granule binding. However, Hide discloses e.g., at page 488, col. 2 that cells (mast) contain large numbers of secretory granules which makes them highly refractile which is manifested in the light-scattering properties of the cells, particularly at around 90 degrees. When the cells have undergone exocytosis, their refractivity is lost and their ability to scatter light at 90 degree is correspondingly diminished. This attribute has been used to classify populations of (mast) cells. Applicants at page 38, lines 10-20 admit that annexin is commercially available. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to measure the cellular phenotype alteration in the method of Nolan by exocytosis by annexin granule binding since exocytosis measured by granule binding is one of the means of classifying cell populations as taught by Hide (and appears to be a sensitive measure of the cell behavior as shown by its high refractile property).

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is (571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

tdw
September 29,2006